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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,358	MIGALY, PETER	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *May 1, 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,41-43 and 48-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,41-43 and 48-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *May 1, 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted May 1, 2008, wherein claims 1-3, 36, 54, 57, 95, 108, 122, 123, and 130 are amended and new claims 131-143 are introduced. This application claims benefit of provisional application 60/319436, filed July 30, 2002.

Claims 1-38, 41-43, and 48-143 pending in this application.

Claims 1-38, 41-43, and 48-143 as amended are examined on the merits herein.

The following new grounds of rejection are introduced:

Claim Objections

Claims 6, 9, 10, 12, 14-35, 37, 41-43, 48, 49, 51-56, 58-94, 96-107, 109-121, and 124-129 are objected to because of the following informalities: the claims contain underlining and strikethroughs to indicate amendments to the claims even though these claims have not been amended in the most recent amendment. This notation creates confusion as to which claims have been amended since the most recent amendment. Rather, underlines and strikethroughs should only be used to indicate the changes made to the claims in the **most recent** amendment. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 140, 141, and 143 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims contain long, rambling arguments and run-on sentences that make the scope of the claims extremely difficult to understand. It is unclear what practical limitations if any are intended by the argumentation, and the claims as currently written are so confusing that one skilled in the art would not be able to ascertain the true scope of the claims. If the sole point of the argumentation is to support Applicant's arguments as to the patentability of the claims, then it should be included in the body of Applicant's arguments/comments. If these arguments are intended to outline a specific set of rationales that the practitioner should discuss with the patient, they should be presented in a more organized and concise form.

Additionally, it should be noted that motivations and mental processes are not in themselves patentable. What is patentable is the concrete result issuing form said motivation or mental process.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 11, 13, 37, 38, 41-43, 48, 49, 53, 54, 56, 58, 59, 119-121, 123, 126-129, and 140-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howard. (US patent publication 2002/0123490, cited in PTO-892)

Howard discloses a combination of a serotonin reuptake inhibitor and an atypical antipsychotic, as well as a method for using this combination to treat obsessive compulsive disorder, psychosis, and depression. (p. 1, paragraph 0004) Depressive disorders treated include major depressive disorder, as well as atypical depression including anxiety. (p. 1, paragraph 0008) Anxiety is reasonably considered to be as cognitive distortion as it involves disordered cognitions such as overestimation of risk. Although treatment of refractory depression is a preferred embodiment, all depression including depression not found to be refractory, is included within the range of disorders to be treated. The amounts of each agent used are such that the combined effect has improved efficacy compared to either component individually. (p. 1 paragraph 0005) Atypical antipsychotics used in the invention include abaperidone, belaperidone, clozapine, iloperidone, olanzapine, perospirone, risperidone, sertindole, tiospirone, ziprasidone, zotepine, quetiapine, and blonanserin. (p. 7 paragraphs 0172-0198) The two agents are to be administered in dosages of about 5-200 mg/day of the antipsychotic agent and about 2.5-500 mg/day of the serotonin reuptake inhibitor. (p. 8 paragraph 0233) The compounds can be administered by various dosage forms including oral administration. (p. 9 paragraphs 0235-0236) Howard does not specifically disclose a method wherein the therapeutic agents are administered as soon as possible.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Howard as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Howard already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. Note that "as soon as possible" is an extremely broad limitation that would include practically any method wherein treatment was not deliberately delayed. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 1, 2, 4, 6, 10-15, 18, 22, 26, 30, 36-38, 41, 42, 48, 51-53, 56, 58-60, 109-118, 124, 125, and 140-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefson et al. '921 (US patent 5958921, cited in PTO-892, different from Tollefson WO99/61027 cited previously) in view of the Merck manual of diagnosis and Therapy. (Merck, of record in previous office action)

Tollefson '921 discloses a method of treating major depression comprising administering an effective amount of olanzapine. (column 1 lines 30-55) A dose of 2.5-

30 mg per day is recommended. (column 2 lines 23-25) Olanzapine can be formulated as tablets for oral administration. (column 4 lines 5-25) Tollefson '921 does not disclose a method further comprising administering an antidepressant, for example one of the various serotonin reuptake inhibitors recited in the claims.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with olanzapine as disclosed by Tollefson '921. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Tollefson '921 as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Tollefson '921 and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected

success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer olanzapine in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

The following rejections of record in the previous action are maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-12, 37, 38, 41-43, 48-50, 53-71, 95-103, 126, and 131-143 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal comprising administering certain antidepressants defined in the specification and prior art, does not reasonably provide enablement for such a method

involving any antidepressant whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method of treating depression and other disorders by administering a drug or a combination of two drugs. It is claimed that the antipsychotic drug improves the therapeutic outcome even in patients not suffering from psychotic symptoms.

The state of the prior art: Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art. Although a number of drug combinations have been tested and found to be useful, particularly combinations of a serotonin reuptake inhibitor with an atypical antipsychotic, many drugs of both types have not been tested. In particular, typical antipsychotics and dopamine system stabilizers such as aripiprazole have not been tested in the claimed methods. More

generally, the full limits of the class of compounds known under the various functional groupings (e.g. selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, antidepressants with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, antidepressants with serotonin/norepinephrine/dopamine reuptake inhibition, etc.) recited in the language of instant claim 1 have not been determined, and it is likely that there exist novel compounds with antidepressant activity that have not yet been discovered.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: In the absence of any general theory explaining the action of atypical antipsychotic drugs to enhance therapeutic outcomes with antidepressants, it is not possible to predict the efficacy of any particular antipsychotic for this purpose absent experimental data. Because so many different compounds are known as antidepressants no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally. Thus the effectiveness of a particular combination therapy of an antidepressant and an antipsychotic for the treatment of depression, cognitive distortions, smoking cessation, or nicotine withdrawal is unpredictable.

The Breadth of the claims: The claimed invention encompasses combination therapies of any of a number of functionally defined groups of antidepressants with an antipsychotic. The antidepressants are defined only by their functional characteristics.

In particular, a vast number of different structures are included within the limits of these claims.

The amount of direction or guidance presented: Two hypothetical cases are given in order to illustrate possible uses of the claimed therapeutic method. (p. 16-17)

The presence or absence of working examples: No working examples of the claimed therapeutic methods are provided by Applicant.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as antidepressant/antipsychotic combination therapy. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention, one skilled in the art would be required to determine the extent of antidepressants useful in said methods. Because Applicant has provided no working examples, and because the state of the art is unpredictable, many different antidepressants would need to be tested in order to provide a comprehensive understanding of which combinations are or are not useful in the claimed method. Because there is no structural limitation to the full scope of the various functionally defined groups of antidepressants, one skilled in the art would have to discover each and every possible compound with antidepressant activity. Doing so would require the synthesis and testing of an enormous number of compounds. In the process of synthesizing the compounds to be tested, many novel and unpredictable synthetic methods would have to be developed. These experiments would be repeated many

times in animal models of depression, cognitive distortions, and nicotine addiction, in order to establish their suitability as therapeutic methods. It should be noted that evaluating psychological disorders such as depression and cognitive distortions in animals is more difficult than evaluating a therapy for a nonpsychological condition such as cancer or arthritis. Animal experiments include, along with the actual administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these animal experiments would need to be repeated many times, and involve the maintenance, killing, and disposal of many experimental animals, to establish the suitability or lack thereof for each compound found to possess the desired activity in vitro.

The scale of synthesis, *in vitro*, and *in vivo* testing described in the preceding paragraphs would present an undue amount of unpredictable experimentation to require of anyone wishing to practice the invention.

Genentech, 108 F.3d at 1366, sates that, “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion.” And “patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.”

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention with all of the compounds falling within the recited functional groupings of antidepressants.

Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted January 8, 2007 with respect to claim 65 has been fully considered and but is deemed to insert **new matter** into the claims since the specification as originally filed does not provide support for the active metabolite of risperidone. As the instant specification as filed contains no description of said metabolite or a method of using it as a therapeutic agent, the specification as originally filed does not provide support for the subject matter of instant claim 65. See *in re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, 109-122, 124, 126-130, and 140-143 are rejected under 35 U.S.C. 103(a) as being obvious over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action)

Chappell et al. discloses a method of treating depression, anxiety, or psychosis in a mammal by administering a combination of an antidepressant, a D4 receptor antagonist, (an antipsychotic) and a pharmaceutically acceptable carrier. (p. 1, left column, paragraph 0002) Note that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Phobias and panic disorders are also considered to be cognitive distortions. General types of antidepressants which can be used are listed in paragraph 0021 and include norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and monoamine oxidase inhibitors, among others, as described in instant claims 11-13. Selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine, and sertaline. (p. 3, paragraph 0025) Norepinephrine reuptake inhibitors which may be used are listed in paragraph 0023 and include clomipramine among others, as in instant claims 14 and 15. Other useful antidepressants are listed in paragraph 0181 on p. 8. The compounds used in this invention may all be administered orally, as described by instant claim 38. (p. 22, paragraphs 0460-0462) Various dopamine D4 receptor antagonists can be used, as listed on pp. 15-21. In particular, p. 20, paragraph 0446 lists olanzapine as a useful D4

receptor antagonist. D4 receptor antagonists can be administered in a preferred dose of about 5 to about 500 mg per day. (p. 22, paragraph 0459) Chappell et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider. Chappell et al. does not disclose a method where in the antipsychotic is administered in a dose of 2.5-10 mg olanzapine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Chappell et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Chappell et al. already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.
It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Chappell et al. using a dose of 5-10 mg of olanzapine per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Chappell et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie

case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Further, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 106-108, 131-134, and 136-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) in view of Berman et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine, which acts on the NMDA receptor, exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as the antidepressant in the method of Chappell et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the antidepressants recited by Chappell et al. One of ordinary skill in the art would

reasonably have expected success because Ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 127 and 128 are rejected under 35 U.S.C. 102(b) as being anticipated by Robertson et al. (Reference of record in previous action)

Robertson et al. discloses a number of studies of the antidepressant activities of major tranquilizers (also known as typical antipsychotics). (p. 173, last paragraph) In particular, perphenazine and combinations of perphenazine with amitriptyline were used in treating patients suffering from depression, including non-psychotic depression. (p. 179, paragraphs 4-5) Perphenazine was found in one study to be particularly effective, while a combination of perphenazine and amitriptyline was found to be effective for treating other types of depression. It is noted that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Flupenthixol, (p. 183, paragraphs 4-6) and sulpride, (p. 185, paragraphs 1-2) are also seen to possess antidepressant activity. The intended uses recited in the instant claims, for example

inhibiting the development of tolerance toward an antidepressant, providing a neuroprotective effect, avoiding worsening of the depression, resisting suicide, avoiding suicidal ideation, and delaying or resisting relapse, are inherently present in any circumstance where the claimed drugs are administered to a patient suffering form depression, as all depressed patients are at elevated risk for suicide, and could suffer relapse after treatment.

Therefore the claimed invention is anticipated by Robertson et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 16, 17, 20, 21, 24, 25, 28, 29, 32-35, 64, 75, 76, 79, 80, 83, 84, 87, 88, 91-94, 123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Schmidt et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using ziprasidone, risperidone, or quetiapine as the antipsychotic agent.

Schmidt et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 198, table 1) In particular, ziprasidone, risperidone, olanzapine, and quetiapine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ziprasidone, risperidone, or quetiapine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 5, 9, 16, 20, 24, 28, 64, 75, 79, 83, 87, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Roth et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using risperidone, trifluoroperazine, or zotepine as the antipsychotic agent.

Roth et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 366, table 1) In particular, risperidone, olanzapine, trifluoroperazine and zotepine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use risperidone, trifluoroperazine, or zotepine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 1-3, 9, 11-15, 37, 38, 41-43, 48, 49, 53-62, 69-74, 96-105, 129, and 141-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in PTO-892) as applied to claims 126-128 above, and further in view of the Merck Manual of Diagnosis and Therapy, Seventeenth Edition. (Reference included with PTO-892, herein referred to as Merck) The disclosure of Robertson et al. is discussed above. Robertson et al. does not disclose a therapy comprising a combination of a typical antipsychotic with a newer antidepressant. (i.e. an

antidepressant that is not a tricyclic or tetracyclic antidepressant or a MAO inhibitor) Robertson et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Robertson et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Robertson et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Robertson et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected

success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in PTO-892) in view of Berman et al. (Reference of record in previous action) The disclosure of Robertson et al. is discussed above. Robertson et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Robertson et al. One of ordinary skill in the art

would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Robertson et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because Ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's argument, filed August 27, 2007, as applied to the above rejection, has been fully considered and not found to be persuasive to remove the rejection, for reasons recited as regards the rejection over Chappell et al. in view of Berman et al.

Claims 1, 2, 4, 5, 6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48, 49, 51-64, 66, 70-77, 79-81, 83-85, 87-89, 91-105, 109-122, 124-129, and 140-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pivac et al. (Reference included with PTO-892) in view of Merck (Reference included with PTO-892) Pivac et al. discloses that atypical antipsychotics such as risperidone or olanzapine, should be coadministered with selective serotonin reuptake inhibitors, because they produce a synergistic effect. (p. 236, left column, last paragraph, right column first paragraph) Pivac et al. does not disclose a therapeutic method using the specific SSRIs fluoxetine, paroxetine, sertaline, or fluvoxamine, or the atypical antipsychotics ziprasidone or quetiapine. Pivac et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to

a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine. Merck et al. also discloses a listing of atypical antipsychotics, including clozapine, risperidone, olanzapine, quetiapine, sertindole, and ziprasidone. (p. 1570, table 193-4)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the various SSRIs and atypical antipsychotics disclosed by Merck in the method of Pivac et al. One of ordinary skill in the art would have recognized that the specific compounds disclosed by Merck fall within the broad classes described by Pivac et al., and can thus be used in the disclosed method. Substituting these known prior art compounds in a known prior art method is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Pivac et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Pivac et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success

because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves.

Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 1-4, 7, 8, 10-15, 19, 23, 27, 31, 36-38, 41-43, 48, 49, 51-63, 67, 68, 70-74, 78, 82, 86, 90, 95-105, 109-122, 124-130, and 140-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (PCT international publication WO02/060423, reference included with PTO-892) in view of Merck. (Reference included with PTO-892) Jordan et al. discloses a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor, comprising administering a compound having a given structure. (p. 15, lines 5-18) According to the Chemical Abstracts Registry entry 129722-12-9, (reference included with PTO-892) this

structure is aripiprazole. This compound is useful for treating various disorders of the central nervous system, for example major depression and melancholia, as well as various cognitive distortions including obsessive compulsive disorder, alcohol and drug addiction, and cognitive impairment. (p. 16, line 23 – p. 17, line 10) The preferred unit dosage form is 1-20 mg of active agent. (p. 18, lines 5-10) Jordan et al. does not disclose a method comprising administering aripiprazole in combination with an antidepressant. Jordan et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering 2.5-15 mg of aripiprazole.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Jordan et al. to a patient suffering from major depression either alone or complicated by any of the various cognitive distortions recited by Jordan et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Jordan et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Jordan et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Jordan et al. using a dose of 2.5-15 mg of aripiprazole per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Jordan et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 106-108, 131-133, and 135-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (Reference of record in PTO-892) in view of Berman et al. (Reference of record in previous action) The disclosure of Jordan et al. is discussed above. Jordan et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Jordan et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Jordan et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 3-5, 9-15, 20, 28, 37, and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Theobald et al. (US patent publication 2003/0049308, first published as PCT international publication WO01/80837) Theobald et al. discloses a transdermal or transmucosal patch comprising nicotine and a further active substance, that is useful for treating nicotine dependency, for nicotine substitution, or for disaccustoming smokers. (p. 1, paragraphs 0002, 0003, and 0009) The additional active agent can include antidepressants or neuroleptics (antipsychotics), for example chlorpromazine, perphenazine, sulpride, clozapine, clomipramine, doxepin, risperidone, paroxetine, or fluvoxamine. (p. 2, paragraphs 0015-0017) Theobald et al. does not explicitly exemplify a method comprising administering said patch comprising nicotine, an antidepressant, and an antipsychotic.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Theobald et al. using nicotine in combination with both an antidepressant and an antipsychotic. One of ordinary skill in the art would have been motivated to practice the invention in this manner because each of the additional agents (the antidepressant and the antipsychotic) is revealed individually by Theobald et al. to be useful in combination with nicotine for the treatment of nicotine addiction. Adding both of these agents at once to the disclosed invention is well within the ordinary and routine level of skill in the art and carries a reasonable expectation of success in achieving the desired therapeutic goal.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument

Applicant's arguments, submitted May 1, 2008, with respect to the various grounds of rejection above, have been fully considered and not found to be persuasive to remove the rejections. Reasons that the arguments were not found to be persuasive are discussed below:

General issues raise by Applicant

Before addressing the specific grounds of rejection under consideration, several issues will be explained in order to clarify the reasons for the pending rejections.

Firstly, as stated in the previous office action, the Patent Office is a fundamentally different institution from the Food and Drug Administration. The FDA is concerned primarily with the efficacy and safety of new drugs, and makes a judgment based on whether a drug is safe and effective compared to the current standard of care. The Patent and Trademark Office, by contrast, is concerned with whether a claimed invention represents a novel and non-obvious discovery over the prior art. In order to be regarded as enabled a reference (for example Chappell et al.) must merely describe a process that one skilled in the art could carry out with a reasonable expectation of success. The fact that, for all practical purposes, FDA regulations and malpractice lawsuits would make it impossible to carry out the method in actual clinical practice today does not remove the reference as prior art. It merely indicates that the prior art method is one which the medical profession has decided not to utilize because other

therapies, such as antidepressant monotherapy, are judged to be preferable given current priorities.

Secondly, routine modification of the prior art, or choosing from various options presented in the prior art, is not in itself patentable. Most clinicians would choose to give a depressed patient a single antidepressant as initial therapy, in order to minimize the risk of side effects. Applicant would choose to give the patient an antidepressant plus an antipsychotic, in order to minimize the risk of suicide. Both approaches can draw support from the prior art, although the FDA and most malpractice juries would side with the monotherapy. If the claimed invention is merely a routine modification of the prior art, involving the manipulation of routine result-effective parameters such as dosage level, route of administration, or timing of administration, or the combination of two or more prior art inventions known to be useful for the same purpose or otherwise compatible, the invention is *prima facie* obvious. The patentability of a *prima facie* obvious invention depends on the presence of secondary considerations, most notably any surprising or unexpected results stemming from Applicant's modification of the prior art. According to MPEP 2145:

> Rebuttal evidence may include evidence of "secondary considerations," such as "commercial success, long felt but unsolved needs, [and] failure of others." Graham v. John Deere Co., 383 U.S. at 17, 148 USPQ at 467. See also, e.g., In re Piasecki, 745 F.2d 1468, 1473, 223 USPQ 785, 788 (Fed. Cir. 1984) (commercial success). Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. Dillon, 919 F.2d at 692-93, 16 USPQ2d at 1901. A showing of unexpected results must be based on evidence, not argument or speculation. In re Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997)

For example, the discovery that administering two agents together produces a synergistic effect with more than additive results, could possible overcome a case of *prima facie* obviousness. In the instant case, Applicant has repeatedly asserted that the combination of an antidepressant and an antipsychotic is especially effective at reducing the risk of suicide. If this effect is an unexpected result over the prior art, Applicant must provide evidence of this effect in order for it to be considered as a secondary factor affecting patentability. The specification as originally filed has no evidence of any experimental results. Note that further data can be submitted in a declaration under 37 CFR 1.132 in order to establish secondary considerations.

Thirdly, a characteristic that is inherent in a particular invention, for example the effect produced by administering a particular compound to a particular subject, does not render a claim patentable over the prior art. See *Ex parte Novitski* 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993). Note that the claiming of a new use, new function, or unknown property which is inherently present in the prior art does not make the claim patentable. See *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also *Eli Lilly and Co. v. Barr Laboratories Inc.* 251 F3c. 955; 58 USPQ2d 1869-1881 (Fed. Cir. 2001) with regard to inherency as it relates to the claimed invention herein. The fact that the claims recite specific motives (e.g. resisting suicide, delaying relapse, avoiding sensitizing a patient to depression) does not serve to differentiate the claims from the prior at unless these motives are manifest in an actual difference in the way the method is performed as compared to the prior art.

Rejection of claims 1-9, 11-12, 37, 38, 41-43, 48-50, 53-71, 95-103, and 126 under 35 USC 112, first paragraph

Applicant has amended these claims to recite certain specific functionally defined groups of antidepressants. However, the problem with the enablement of these classes of drugs is not overcome by the amendment. Essentially, the lack of enablement for functionally-defined groupings of compounds stems from the fact that these groups are open-ended and contain a wide variety of structurally unrelated compounds. Any attempt by one skilled in the art to practice the full scope of the invention would require one to make and test a huge number of compounds that are not yet known in the chemical literature. In fact, for most chemical compounds, it is not known whether they are serotonin reuptake inhibitors, serotonin agonists, NMDA receptor antagonists, etc. Therefore it would be necessary to obtain all of these compounds, either by synthesizing them or by isolating them from a natural source. Either manner of obtaining them would present an undue burden of unpredictable experimentation. In general, this problem exists for any class of compounds that is defined by its function rather than its structure. In order for one skilled in the art to be able to obtain a representative sample of the full scope of the claimed class, the class of compounds must be recognized in the art as being associated with a particular structural limitation. (e.g. benzodiazepines) The claims as currently amended do not fulfill this requirement. Therefore the rejection is maintained. If Applicant believes the current functional language is acceptable, he should present evidence that one skilled in the art would regard each of the claimed classes as being limited to particular structural features.

Rejection of claim 65 under 35 USC 112, first paragraph

Applicant argues that the medicinal effect of fruit and fruit juice is the same. By way of rebuttal, two references are presented (Whfoods, American Academy of Pediatrics, particularly p. 1211, left column "Juice in the Food Guide Pyramid," and p. 1212, left column "Conclusions," references included with PTO-892) indicating that fruit juice cannot replace whole fruit in the diet, and that fruit juice lacks the nutrients, such as fiber and water-soluble vitamins, that are found in whole fruit. It is also noted that the metabolism of drugs is expected to be a much more complicated process than the squeezing and juicing of fruit, and to therefore be all the more complex and unpredictable. Because each product is transformed in a way that would affect its suitability for its intended purpose it cannot be regarded as being identical to the unprocessed product.

Applicant further argues that the finding of additional advantages and secondary factors would serve to grant patent protection to a hypothetical future inventor who actually discovers an active metabolite of risperidone, thus preserving the incentive for future research in this area, and that the Office's alleged concern for said incentives is inconsistent with the alleged lack of concern for the incentives involved with the present invention. However, the discussion of the amount of research performed by drug companies on prodrugs was not presented in order to argue that drug companies need intellectual property incentives to perform such research. Rather it was presented in order to demonstrate that prodrugs are not identical to their active metabolites, as if this

were the case most pharmaceutical companies would be wasting significant resources to discover a new compound that is exactly identical to an old compound. The entire field of prodrug research is based on the fact that a prodrug is not the same as the active metabolite and that administering one is not the same as administering the other.

The written description standard requires that every element of the claims be described in the specification as originally filed in such a way as to indicate that Applicant was in possession of the claimed invention with all the claim limitations. The specification as originally filed does not describe the active metabolite of risperidone, or active metabolites in general. Therefore this claim lacks written description in the specification. Furthermore, even if correct, Applicant's arguments would not render the invention patentable. Given the absence of any new teaching in the specification on this active metabolite, even if the active metabolite of risperidone were shown to be substantially identical to risperidone, then any mention of risperidone in the prior art would inherently be prior art against the claimed invention. If making and using an active metabolite were a simple, predictable, trivial modification of a parent compound, then this claim would be obvious over prior art methods involving risperidone. The reason that these rejections were not made is because risperidone and its active metabolite are not in fact identical.

For these reasons the rejection is maintained.

Rejection of claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, 109-122, 124, and 126-130 under 35 USC 103(a) as being obvious over Chappell et al.

Applicant argues that dopamine D4 receptor antagonists are not necessarily antipsychotic drugs, and presents the Kramer reference to demonstrate this fact. However, Chappell et al. lists an extensive number of specific dopamine D4 antagonists that can be used in this invention, some of which are unquestionably antipsychotics. For example, p. 20, paragraph 0445 of Chappell et al. cites the compound PNU-96415E and incorporates by reference the disclosure of Tang et al. (Reference included with PTO-892) Tang et al. discloses that this compound demonstrates antipsychotic activity in an accepted animal model of psychosis. (p. 442, right column, p. 443, left column) Furthermore paragraph 0446 of Chappell et al. lists olanzapine, which is admitted by Applicant to be an antipsychotic agent. Other D4 receptor antagonists that are recited by Chappell et al. and which are antipsychotic agents include the compounds of US patents 5883094 (see column 4 lines 5-10 of 5883094) 5432177 (column 1 lines 50-59) and 5633376 (column 3 lines 28-38) for example. Therefore Chappell et al. specifically discloses dopamine D4 receptor antagonists that are in fact antipsychotic agents.

Applicant further claims that treatment of anxiety is different from treatment of cognitive disorders. However, while factors other than cognitive distortions are involved in anxiety, cognitive distortions are an important and essential part of anxiety disorders. In support of this conclusion, Applicant makes the assertion that anxiety in certain circumstances, such as a totalitarian society or a dysfunctional work environment, is a

rational response involving no disordered cognition. However, anxiety in the sense used in the Chappell et al. reference clearly refers to **pathological** anxiety disorders and not to a healthy response to stressful situations. P. 1, paragraph 0010 of Chappell et al. lists specific instances of anxiety as including, "anxiety **disorders**, such as panic **disorder**, with or without **agoraphobia**, agoraphobia without history of panic disorder, specific **phobias**," and so on. The very fact that the reference is concerned with a therapeutic method indicates that the conditions being treated are pathological conditions. Otherwise no therapeutic solution would be needed. Thus the instances of anxiety described by Chappell et al. are clearly pathological anxiety disorders and not ordinary stress.

Furthermore, the references Casey et al., Ost et al. and Uhlenhuth et al. (included with PTO-892) disclose that anxiety disorders, panic disorders, and claustrophobia involve significant contributions from a disordered or abnormal cognitive style characteristic of anxious or phobic individuals. For example the survey items in appendix A of Uhlenhuth et al., which are used to diagnose a characteristic anxiety-prone cognitive style, includes questions regarding perceptions of positive and negative events, and the importance a patient attaches to future worries. The anxious cognitive style described by this reference fits within the definition of cognitive distortion as including such features as " overgeneralization, all or nothing (always-never) thinking, discounting positives or negatives, blaming and "labeling", assumptions and predictions, and emotional reasoning, all of which lead to "jumping to conclusions", without analysis of the facts," as described in the specification, p. 15, lines 9-13. Furthermore the

reference Sharp et al., included by Applicant with PTO-1449 discloses that cognitive behavioral therapy improved the symptoms of panic disorder. Because CBT is focused on correcting cognitive distortions, its effectiveness indicates that cognitive distortions are present in panic disorder. For these reasons the pathological anxiety and panic disorders described by Chappell et al. are seen to involve cognitive distortions. Note that the term "cognitive distortion" even taken in its specific clinical definition, is rather broad and many if not most psychiatric disorders involve some sort of distorted cognition.

With regard to Applicant's reference to the previous equation of depression with cognitive distortion being withdrawn, this argument is not persuasive in view of the cited prior art, namely the presence of distorted cognitive style in patients suffering from anxiety disorder and the effectiveness of cognitive behavioral therapy in reducing the symptoms of anxiety disorder.

Applicant further argues that the prior art does not disclose any pharmacological treatment of cognitive distortions. The prior art includes many instances in which antipsychotic medication is used to treat disorders such as anxiety, schizophrenia, or obsessive compulsive disorder, that include distorted cognition as part of their pathology. According to MPEP 2145, Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979) The fact that Applicant has concluded that antipsychotic drugs act to remove disordered cognition when administered for treating depression, anxiety, or the like does not constitute a patentable invention.

Still further, Applicant argues that the fact that cognitive behavioral therapy combined with pharmacotherapy yields a benefit over CBT alone is persuasive to show that anxiety disorders are not equivalent to cognitive distortions. Firstly, no treatment is 100% effective. Because of this it is reasonable to expect that even patients undergoing CBT will have some residual cognitive distortion and anxiety that would be further corrected by pharmacotherapy. Secondly, it is not necessary to show that anxiety and cognitive distortion are 100% identical, merely that disordered cognition is one component of anxiety disorders.

Applicant also argues that there is a difference between the obvious prior art practice of administering a drug as soon as it is indicated and the claimed practice of administering the drug as initial therapy or as soon as possible. First, the phrase, "as soon as possible" is a broad limitation that encompasses a treatment algorithm whereby treatment is given as soon as indicated. It is not possible under such an algorithm to administer treatment before it is indicated. Because Applicant does not specify what sort of possibility is meant by “as soon as possible” this limitation is so broad as not to meaningfully limit the claim. Secondly, the fact that practitioners in the art regard a specific invention (administering the therapy as described by Chappell et al. as an initial therapy) to be inferior to another therapy does not render it patentable. It is clear from the disclosure of Chappell et al. that administering a combination therapy for depression gives an added benefit over administering a monotherapy, otherwise the reference would not recommend administering an additional drug when an antidepressant alone would be just as effective. Those of ordinary skill in the art generally avoid doing so

anyway because of the side effects of antipsychotic drugs, but are in fact aware that this option exists in theory.

Applicant further argues that the differences in doses between the claimed invention and the prior art are crucial to the function of the invention. How is the difference in dose crucial? Applicant has cited no evidence that combining an antidepressant and an antipsychotic allows the antipsychotic to be administered at a lower dosage. In fact, no experimental data is presented at all that would designate this variable as being crucial.

Applicant further argues that the claimed invention involves a new risk-benefit analysis that is not known in the prior art. However, the specification as originally filed does not discuss any risk-benefit analysis or give any evidence that this is the crux of the invention. Rather the specification merely states (without any evidence other than the prior art) that an antidepressant and an antipsychotic can be co-administered in order to reduce the risk of suicide in patients suffering from depression. The extent of Applicant's new cost-benefit analysis appears to be that the risk of suicide is so great that an aggressive treatment including an antipsychotic treatment is warranted in any case of depression even in light of the side effects of antipsychotic drugs. This is not an invention, it is a judgment call. As has been stated before, the mere fact that the invention is regarded by those of ordinary skill in the art as inferior to another approach does not render it non-obvious.

Applicant's arguments appear to stand on two assertions - that the Chappell et al. reference fails to provide enablement for treating depression because one of

ordinary skill in the art would regard administering an antipsychotic to a non-psychotic depressed patient who had not shown resistance to antidepressants as malpractice, and secondly that the fact that Applicant's method is undertaken for the purpose of reducing the risk of suicide according to a cost benefit analysis that rates the cost of suicide more highly than the prior art cost benefit analysis.

As regards the first assertion, it has been repeated that just because practicing an invention would be unethical, illegal, prohibitively expensive, risky, immoral, or otherwise undesirable does not mean that it cannot be patented, or cannot serve as prior art during patent prosecution. The enforcement of such considerations is left up to other agencies. Otherwise the enablement and non-obviousness of an invention would depend on the regulatory and liability environment at the time. Furthermore, as Applicant has provided no additional evidence or data concerning the claimed method beyond what is known in the prior art, this assertion amounts to saying that coadministering these two agents is malpractice when someone else does it but is not malpractice when Applicant does it.

As regards the second assertion, the **invention as claimed** does not disclose any cost benefit analysis. The claims do not contain a cost benefit analysis. The only mention of cost benefit analysis is in Applicant's arguments during prosecution in an attempt to differentiate the claimed invention from the prior art. One of ordinary skill in the art reading the instant disclosure would have no idea that he is supposed to undertake a specialized cost benefit analysis in order to justify the claimed invention. In fact, there is no way for Applicant to know whether the attorney prosecuting the

Chappell et al. patent did not make an identical argument concerning the risk of suicide during the prosecution of said application. Arguments made during prosecution do not constitute a feature of the claimed invention if they are not included as claim limitations. Thus **if practicing the invention of Chappell et al. is malpractice then practicing the present invention is malpractice as well** since one of ordinary skill in the art reading the instant claims would not be directed to undertake any cost-benefit analysis. Therefore this so-called feature does not serve to distinguish the invention from the prior art.

Note that any attempt to introduce a cost-benefit analysis into the claims, as is the case with new claims 140, 141, or 143, would be rejected under 35 USC 112 as introducing new matter into the disclosure and lacking written description ins the specification as originally filed, Because the cost-benefit analysis is not described in the claims.

In sum, the only "teaching against" practicing the invention of Chappell et al. in a manner that renders the claimed invention obvious is the fact that the current state of the art strongly considers monotherapy to be a better approach as initial therapy. In theory, the only thing keeping one of ordinary skill in the art from using combination therapy is the collective judgment of those in the art that any improved efficacy is not worth the increased side effects. One of ordinary skill in the art would have various reasons to use the combination therapy of Chappell et al., for example if the patient were immanently suicidal or expressed a strong desire to get better as soon as possible

even given the risks of antipsychotic drugs, or if the practitioner were concerned that he case of depression may turn out to be refractory to monotherapy.

Applicant further asserts that his own method would not be subject to charges of malpractice because of the risk/benefit analysis that he would undertake. Any practitioner would undertake a risk/benefit analysis before administering therapy. There is nothing special about Applicant that makes his risk/benefit analyses especially valuable or persuasive. Why has Applicant chosen to second-guess the existing thinking about antipsychotic risks and benefits in depression? Because he believes that the expected benefits are worth the expected risks. That is a decision, not a discovery, and it does not rise to the level of novelty or unobviousness needed to be patentable. The fact is, all that separates Applicant's reasoning from the prior art reasoning is that Applicant is more worried about suicide and less worried about tarditive dyskinesia and other side effects. Any practitioner having the same priorities would come to the same conclusion. If it would be impossible for one of ordinary skill in the art to practice a combination therapy for treating depression, than it would be impossible for Applicant as well. Both the specification as originally filed and the provisional application 60/319436 rely for their reasoning on a collection of various prior art references on the treatment of depression, the risk of suicide, and the benefit of antipsychotics. Applicant is relying **entirely** on what is known in the prior art about therapy of depression for enablement, and simply coming to the conclusion that there would be a sufficient benefit to aggressively treating depression to warrant using a more aggressive therapy initially. If Applicant had shown that the risks of antipsychotics were less than was believed in the

prior art, or that the benefits were greater, or that this method were unexpectedly effective in reducing suicide among depressed patients, then this showing might be evidence of secondary consideration. Otherwise there is no additional element that is not obvious from the prior art.

Applicant further argues that a risk/benefit analysis is patentable, as demonstrated by the instance of clozapine. However, the three PCT international **publications** WO96/31621, WO9721833, and WO97/32037 cited by Applicant are not patents. They are international **applications** filed under the Patent Cooperation Treaty that carry no intellectual property privileges and merely serve as priority documents for national phase applications. Thus their existence proves that someone filed for a patent on a cost/benefit analysis but not that said patent was granted. Note that none of these applications resulted in the grant of a US patent. Also note that assessing a patient's response to a therapy is different from administering the therapy itself, which is what is being claimed in the instant claims. Similarly, the instant claims are not related to a method of ameliorating side effects or monitoring side effects from a therapy, or of specifically administering the therapy to a group of patients who would derive the greatest benefit. It appears that the later patents for clozapine referred to by Applicant are US patents 5563134 and 5312819, (References included with PTO-892) which claim compositions and methods further comprising and **additional** ingredient that ameliorates the adverse effects, and US patent 6197764, which claims a conjugate of clozapine with a fatty acid. Neither of these patent are analogous with the claimed invention as they introduce additional limitations over the prior art, namely modifying the

structure of clozapine or adding an additional element to the pharmaceutical formulation. In any case, Applicant has not identified any granted US patent claiming a cost/benefit analysis. Furthermore, note that 3539573 claims priority all the way back to the original invention of Clozapine in Aug. 16, 1960, (thus it is the original Clozapine patent) and 3962248 claims a process of making clozapine, and not the compound itself. Furthermore note that at the time 3962248 was issued the patent term in the US was 17 years from the date of issue, rather than the current term of 20 years from the filing date. Therefore it would have expired on June 8, 1993, 31 years after clozapine was invented. Because of the delay in prosecution that can occur, patents issued during that time period (so-called "submarine" patents) could often have an expiration date many decades after their original priority date. Therefore the late expiration of a patent on Clozapine does not prove that the Office issued a second patent on the same medication in view of a new cost-benefit analysis.

Applicant further argues that the reasoning used in the rejection would render obvious a (putatively ridiculous) therapy involving 20-30 different medications and anticonvulsant therapy. Such a therapeutic method would in fact probably be considered enabled by the Office. What stops physicians from practicing it is not the disapproval of the USPTO but rather the ordinary and routine cost-benefit analysis performed by any physician before administering a therapy. It is indeed obvious to combine any number of existing therapies **because one of ordinary skill in the art would be able to tell if doing so was warranted and to refrain from doing so if it was not.**

Applicant also argues that various additional properties recited in the claims are not inherent because the prior art did not describe or understand that all of these additional properties were considered inherent. Applicant appears to misunderstand the nature of inherency. It is not necessary that the prior art recognize an inherent property. Rather **all that is necessary is that the prior art teach a method that would in reality possess the claimed effect** whether or not the effect is explicitly disclosed. In the instant case, the prior art describes administering the same two compounds to the same patient population. If the effect exists in the claimed invention it exists fir the prior art method as well, as the effect of practicing the same method will not depend on whether the practitioner read about it in the Chappell et al. reference or the instant application. This method would inherently produce the claimed results as it is substantially identical to the claimed invention.

Applicant argues that inherency is disproven by the Simon et al. reference that shows that combining benzodiazepam with an antidepressant does not lead to any reduction in relapse of panic disorder. This argument concerns benzodiazepam which is not a compound used by Chappell et al. or the instant claims. Thus it does not disprove inherency.

Applicant further argues that using a low dose of antipsychotic agent would not be obvious. However in the absence of unexpected results or other secondary considerations, one of ordinary skill in the art would be able to select an appropriate dosage level from the teaching of the prior art. Note that paragraph 0459 of Chappell et al. discloses a dose of about 0.05-1500 mg for the dopamine D4 antagonist and

indicates that lower dosages can be used in some circumstances. P. 15, lines 1-2 of the original specification indicates that a low dosage is 25-50 chlorprobazine equivalents, or 100-150mg chlorpromazine equivalents Q.D. Olanzapine, as discussed earlier, is mentioned as a dopamine D4 agonist by Chappell et al. P. 1570 of Merck (of record in previous action) indicates that 4 mg olanzapine is equivalent to 100 mg of chlorpromazine. Therefore 25-50 or 100-150mg chlorpromazine equivalents of olanzapine is about 1-2 or 4-6mg olanzapine, which falls within the general teaching of Chappell et al. Furthermore Merck discloses (pp. 1568-1570) significant side effects, and further suggests (p. 1571, left column, first paragraph) that for maintenance therapy the lowest dose possible should be administered. In view of these teachings of the prior art, lowering the dose would be seen as a routine modification of the prior art. It is common sense that lower doses of a drug produce less serious side effects and that the minimum effective dose should generally be used for drugs with serious side effects.

Finally, Applicant argues that Chappell et al. does not specifically disclose non-psychotic, non-treatment-resistant depression as a specific category of depression. However, Chappell et al. discusses depression and psychosis as two different categories, and even refers to them in the alternative (depression **and/or** anxiety **and/or** psychosis) in paragraph 0020. As regards non-treatment-resistant depression, one skilled in the art, reading the disclosure of Chappell et al., would interpret it as applying to all types of depression and not just treatment resistant depression. There is nothing about the disclosure of Chappell et al. that would lead one skilled in the art to conclude that the teaching of depression only applies to depression hat is treatment-resistant.

With regard to the rejection over Tollefson et al., this rejection was withdrawn because Tollefson et al. specifically targeted only treatment-resistant depression. Chappell et al. does not limit the disclosure to treatment resistant depression.

To summarize, Applicant's claimed invention is based on practicing a nonpreferred variation of the known prior art, namely administering combination antidepressant/antipsychotic therapy as initial therapy in order to treat depression more aggressively so as to reduce the risk of suicide. The prior art is aware that combination therapy exists, but it is not used in actual clinical practice as a first-line treatment because of the side effects of antipsychotics. Applicant argues that it should be used as a front-line therapy because avoiding suicide is more important than avoiding the side effects of antipsychotics. Applicant presents no evidence for this proposition, but rather argues based on what is already known in the prior art. The "invention" in this case is merely a shift in priorities from minimizing harm to maximizing benefit. A shift in priorities is not patentable unless it results in an unexpected benefit. In the instant case, Applicant does not show any unexpected benefit but rather theorizes that his priorities would lead to fewer suicides because of less time waiting for a therapeutic benefit. This is not a sufficient secondary consideration to overcome the *prima facie* case of obviousness.

For the reasons discussed above, the rejection is deemed to be proper and maintained.

Rejection of claims 106-108 as obvious over Chappell et al. in view of Berman et al.

Applicant restates arguments applied to Chappell et al. alone and repeats the assertion that he has presented a "vast amount of secondary factors". These arguments are not found persuasive for the same reasons discussed above. No additional arguments are made beyond saying that what has been stated previously applies further to ketamine.

Furthermore, Applicant's use of ketamine is based merely on a couple sentences in the specification that mention ketamine as an antidepressant. Using ketamine is only enabled because of the evidence in the prior art that it is an antidepressant. If the prior art such as Berman et al. is not enabling for the antidepressant effects of ketamine then there would be no basis for Applicant's use of ketamine either.

Rejection of claims 126-128 as anticipated by Robertson et al.

Applicant argues that anxiety is not a cognitive distortion. This has already been addressed above in the response to the arguments concerning Chappell et al.

Applicant also argues that if Robertson et al. would anticipate the instant claims it would also anticipate the Tollefson et al. patent. The "Tollefson et al. patent" (WO99/61027) is not a patent. It is an international application published under the Patent Cooperation Treaty, an international organization outside the jurisdiction of the USPTO. While it could serve as a priority document for a US patent application, it is not itself a patent and never issued as a patent. Therefore it is not relevant to determining

the standards used by the USPTO. Furthermore, each case is examined on its own merits. Examination is guided by the patent statute and the Manual of Patent Examination and Procedure (MPEP), not by precedent from earlier cases.

Applicant further argues that Robertson et al. reference has been rendered obsolete by progress in antidepressant therapy. However, a rejection for anticipation under 35 USC 102(b) is a statutory bar and no secondary considerations can serve to overcome it. All that matters is the literal teaching of Robertson et al. and whether it fall within the limits of the claimed invention.

As regards claim 126, this claim is no longer rejected on these grounds as amitriptiline is not seen to be included within the scope of claim 126.

As regards inherency, initial treatment, and low dose administration, inherency is discussed previously, and claims 127 and 128 to not require low dose treatment or treatment as initial therapy.

Rejection of claims 5, 16, 17, 20, 21, 24, 25, 28, 29, 32-35, 64, 75, 76, 79, 80, 83, 84, 87, 88, 91-94, 123, and 125 under 35 USC 103(a) over Chappell et al. in view of Schmidt

Applicant argues that this rejection is overcome by the arguments against the rejection over Chappell et al. alone. These arguments are discussed above.

Rejection of claims 5, 9,16,20, 24,28,64, 75, 79, 83,87, and 125 under 35 USC 103(a) over Chappell et al. in view of Roth

Applicant argues that this rejection is overcome by the arguments against the rejection over Chappell et al. alone. These arguments are discussed above.

Rejection of claims 1-3, 9, 11-15, 37, 38, 41-43, 48, 49, 53-62, 69-74, 96-105, and 129 under 35 USC 103(a) as obvious over Robertson et al. in view of Merck

Applicant argues that if Robertson et al. were prior art the Tollefson et al. "patent" would never have issued. This argument, and other arguments concerning initial treatment, low dosage, and inherency, have been addressed previously.

Applicant further argues that Robertson et al. has been rendered obsolete by new developments in the field of pharmacotherapy and that one of ordinary skill in the art would not have applied it at the time of the invention. According to MPEP 2123, "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) The fact that safer drugs were known at the time does not mean that one of ordinary skill in the art could not have combined a typical antipsychotic with an antidepressant. It merely means that those at the time of the invention **chose** not to. While this case of *prima faice* obviousness could be overcome by the presentation of concrete data showing some unrealized benefit from combining the two drugs, Applicant has not shown any such benefit.

Rejection of claims 106-107 under 35 USC 103(a) as obvious over Robertson et al. in view of Berman et al.

Applicant argues that this rejection is overcome by the arguments against the rejection over Robertson et al. alone. These arguments are discussed above.

Rejection of claims 1, 2, 4, 5, 6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48, 49, 51-64, 66, 70- 77, 79-81, 83-85, 87-89, 91-105, 109-122, and 124-129 under 35 USC 103(a) as obvious over Pivac et al. in view of Merck.

Applicant argues that the Ferris et al. reference proves that thinking about the action of antidepressants needs to be reevaluated, thus casting doubt on the teaching of Pivac et al. about antidepressants. However, Ferris et al. was published in 1983, 19 years before the publication of Pivac et al. and more importantly before the widespread use of SSRIs as antidepressants. The antidepressants discussed by Ferris et al. are other types of antidepressants, such as MAO inhibitors. This is shown by the fact that Ferris et al. never mentions serotonin reuptake inhibition or compares bupropion to a serotonin reuptake inhibitor. At the time of publication, zimelidine was the only SSRI available and had just been marketed for about one year. Fluoxetine would not be introduced into the marked for several years yet. Therefore the teaching of Ferris et al. is not seen to contradict or cast doubt on the teaching of Pivac et al. concerning SSRI antidepressants.

Applicant further cites several other references to show uncertainty as to the reasons for the synergistic effects observed between certain antipsychotics and antidepressants. However, uncertainty only overcomes a case of obviousness if it is sufficient to cast into doubt whether there would be any reasonable expectation of

success using the invention. Merely showing that the method by which an invention works, as is the case with the Toth, Roth, and Cremers articles, is not fully known does not keep one of ordinary skill in the art from using it. Furthermore, The cited prior art does not show that atypical antipsychotics to not work to augment the effects of antidepressants but merely that they might exert this effect in a different manner than was supposed by Pivac et al. The one reference showing a clear negative teaching, Perez et al., concerns patients with depression **resistant to SSRIs**. Because the claimed invention specifically deals with non-treatment-resistant depression this teaching that pindolol does not overcome treatment resistance is not relevant to the claims.

The Jordan et al. reference concerns aripiprazole, which has a different method of action from atypical antipsychotics, being a partial agonist of the dopamine receptors. Therefore results concerning aripiprazole are not directly relevant to the atypical antipsychotics which are different molecules with a different receptor profile.

All other arguments made by Applicant have been addressed earlier as applied to other rejections in this action.

Rejection of claims 1-4,7,8,10-15,19,23,27,31,36-38,41-43,48,49,51-63, 67, 68, 7074,78,82,86,90,95- 105,109-122, and 124-130 under 35 USC 103(a) as obvious over Jordan et al. in view of Merck.

Applicant argues that Ferris et al. shows that it is not known how bupropion affects sensitivity to antidepressants. This is not relevant as the rationale for combining

the references is that both drugs are useful individually and thus expected to produce an additive effect when combined. This does not require that the antipsychotic alter sensitivity to the antidepressant. Furthermore as discussed above Ferris et al. was published before the widespread use of SSRI antidepressants or atypical antipsychotics other than clozapine, and does not concern the compatibility of dopamine system stabilizers such as aripiprazole with SSRIs.

Applicant further argues that an analogous compound, busipirone is not approved by the FDA for treating depression and not used off-label for this purpose either. This is not relevant as the standards of patentability used by the PTO are concerned with whether one of ordinary skill in the art **could** practice an invention, not whether those skilled in the art have, collectively, decided not to use a particular therapy as reflected by the decision of the FDA.

Furthermore, the Landen et al. reference is not persuasive to remove the rejection as it concerns the treatment of refractory depression while the claims are drawn to treatment of non-refractory depression.

All other arguments made by Applicant have been addressed earlier as applied to other rejections in this action.

Rejection of claims 106-108 under 35 USC 103(a) as obvious over Jordan et al. in view of Berman et al.

Applicant argues that this rejection is overcome by the arguments against the rejection over Jordan et al. alone. These arguments are discussed above.

Rejection of claims 3-5, 9-15, 20, 28, 37, and 50-52 under 35 USC 103(a) as obvious over Theobald et al.

Applicant complains that no copy of Theobald et al. was enclosed. Theobald et al. is a US patent pre-grant publication and is publicly available to Applicant from the USPTO. Therefore no copy was enclosed with the rejection. In order to expedite prosecution, copies of Theobald et al. and the prior PCT publication have been enclosed with this office action.

Applicant's further arguments were made without reading the reference and are not found persuasive. Specifically, Theobald et al. is enabling because it does in fact disclose both antidepressants and antipsychotics, as discussed in the body of the rejection.

For these reasons all rejections of record in the previous office action are maintained.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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